



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/43 // (A61K 31/43, 31:42)	A1	(11) International Publication Number: WO 98/07424 (43) International Publication Date: 26 February 1998 (26.02.98)
(21) International Application Number: PCT/GB97/02235 (22) International Filing Date: 19 August 1997 (19.08.97) (30) Priority Data: 9617780.3 24 August 1996 (24.08.96) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): BAX, Richard, Peregrine [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). (74) Agent: CONNELL, Anthony, Christopher, SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF A COMBINATION OF AMOXYCILLIN AND CLAVULANATE IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT DRUG-RESISTANT STREPTOCOCCUS PNEUMONIA (57) Abstract <p>Infections potentially caused by DRSP may be treated by a method which comprises administering a pharmaceutical formulation comprising either: for an adult or older child patient from 800 to 1100 mg amoxycillin and from 100 to 150 mg clavulanate in a weight ratio between 6:1 and 10:1 inclusive; or for a paediatric patient from 30 to 40 mg/kg body weight of amoxycillin and from 3 to 8 mg/kg body weight of clavulanate in a weight ratio between 6:1 and 10:1 inclusive; in combination with a pharmaceutically acceptable carrier or excipient, three times a day (tid).</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

USE OF A COMBINATION OF AMOXYCILLIN AND CLAVULANATE IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT DRUG-RESISTANT STREPTOCOCCUS PNEUMONIA

This invention relates to an empiric method of treatment for bacterial infections potentially caused by drug resistant *Streptococcus pneumoniae* using formulations comprising amoxycillin and a salt of clavulanic acid (hereinafter termed "clavulanate" unless a specific salt is identified).

The combination of amoxycillin and clavulanate is an effective empirical treatment for bacterial infections and may be administered by oral dosing, for instance in the form of tablets, and, for paediatric formulations, aqueous solutions or suspensions, typically as a flavoured syrup.

Clavulanate is a β -lactamase inhibitor and is included with the β -lactam antibiotic amoxycillin to counter a β -lactamase mediated resistance mechanism. Some microorganisms such as *Streptococcus pneumoniae* have resistance mechanisms which are not β -lactamase mediated. WO94/16696 discloses generally that potassium clavulanate may enhance the effectiveness of beta-lactam antibiotics such as amoxycillin against microorganisms having a resistance mechanism which is not β -lactamase mediated.

Streptococcus pneumoniae is an important pathogen in respiratory tract infection in the community. *S pneumoniae* is the most commonly implicated bacterium in the important respiratory tract infections of otitis media in paediatrics and sinusitis in patients of all ages and acute exacerbations of bronchitis and pneumococcal pneumonia in adults. There have been increasing reports in Europe and the US of the emergence of DRSP (drug-resistant *Streptococcus pneumoniae*) with decreased susceptibility to β -lactam and other antibiotics.

Whilst confirmed cases of DRSP infection may be successfully treated with relatively high levels of amoxycillin, there still remains the need to develop effective empiric treatments, where DRSP may be suspected, for instance in an area with a high prevalence of DRSP, but where other, β -lactamase producing, organisms may also be present.

International Application WO 97/09042 (SmithKline Beecham Corp) (published after the priority date of the present application) describes formulations for treating DRSP comprising potassium clavulanate and amoxycillin characterised by a relatively high amount of amoxycillin and a twice daily (bid) dosage regimen. Preferred formulations comprise a ratio of 14:1 (amoxycillin:clavulanate), with a typical dosage regimen for paediatrics being 90/6.4mg/kg/day and for adults 3500/250mg/day, taken as as two equal dosages, 12 hours apart (bid).

International Application WO 96/34605 (SmithKline Beecham plc/Corp) (published after the priority date of the present application) describes paediatric

formulations comprising a 7:1 ratio of amoxycillin and clavulanate, for use in a twice daily dosing regimen (bid), such that the total daily dosage is 70/10mg/kg/day.

International Application WO 95/28927 (SmithKline Beecham Corp) describes tablets comprising 875mg amoxycillin and 125mg clavulanate, for use in a bid regimen, such that the total daily dosage is 1750/250 mg/day.

SmithKline Beecham markets in France a paediatric formulation ('Nourrisson') comprising amoxycillin and clavulanate in an 8:1 ratio for use in a thrice daily dosing regimen (tid), such that the total daily dosage is 80/10mg/kg/day.

It has now been found that empiric treatment of infections potentially caused by DRSP may also be successfully treated with formulations of amoxycillin/clavulanate taken three times a day (tid), rather than two times a day, using a lesser ratio of amoxycillin to clavulanate.

Accordingly, the present invention provides a method of treatment of infections potentially caused by DRSP which method comprises administering to a patient in need thereof a pharmaceutical formulation adapted for oral administration comprising either:

- for an adult or older child patient, from 2500 to 3250mg/kg amoxycillin per day and from 350 to 400 mg/kg clavulanate per day in a weight ratio between 6:1 and 10:1 inclusive; or
 - for a paediatric patient, from 75 to 125mg/kg amoxycillin per day and from 12 to 18 mg/kg clavulanate per day in a weight ratio between 6:1 and 10:1 inclusive;
- in combination with a pharmaceutically acceptable carrier or excipient

Suitably, the method is used for the empiric treatment of infections, potentially caused by DRSP, in particular respiratory tract infections such as otitis media in paediatrics, sinusitis and pneumonia in patients of all ages and acute exacerbations of bronchitis in adults

The invention also provides for the use of amoxycillin and clavulanate in the manufacture of a medicament for the empiric treatment of infections potentially caused by DRSP which medicament comprises:

- for an adult or older child patient, from 800 to 1100mg amoxycillin and from 100 to 150 mg clavulanate in a weight ratio between 6:1 and 10:1 inclusive; or
- for a paediatric patient, from 30 to 40mg/kg body weight of amoxycillin and from 3 to 8 mg/kg body weight of clavulanate in a weight ratio between 6:1 and 10:1 inclusive;

the medicament being taken three times a day (tid).

Suitably, the dosage is administered tid, for example in three, preferably equal, unit doses per day, suitably around eight hours apart.

The weight ratios of amoxycillin:clavulanate expressed herein are as free acid equivalent. Preferred amoxycillin:clavulanate ratios are between 6.5:1 to 7.5:1 inclusive, especially about 7:1 or between 7.5:1 and 8.5:1, especially about 8:1.

In the formulations of the invention the amoxycillin is preferably in the form of amoxycillin trihydrate, although sodium amoxycillin, for example the crystalline form of sodium amoxycillin which is disclosed in EP 0131147 A may also be used.

Clavulanate is preferably in the form of potassium clavulanate. Potassium clavulanate is extremely moisture-sensitive and should be stored and handled in conditions of 30% RH or less, ideally as low as possible. Solid dosage forms should be packaged in atmospheric moisture-proof containers, and such forms and/or their containers may contain a desiccant.

Suitably, the dosage is administered in three, preferably equal, unit doses per day, suitably around 8 hours apart

The formulations of the invention may be made up into solid dosage forms for oral administration by a method conventional to the art of pharmaceutical technology, e.g. tablets or powder or granular products for reconstitution into a suspension or solution. Suitable ingredients and suitable methods for making such tablets are disclosed in for example GB 2 005 538-A, WO 92/19227 and WO 95/28927. Powder or granular formulations, such as paediatric suspension formulations, may be manufactured using techniques which are generally conventional in the field of manufacture of pharmaceutical formulations and in the manufacture of dry formulations for reconstitution into such suspensions. For example a suitable technique is that of mixing dry powdered or granulated ingredients for loading into a suitable container.

For paediatric dosing, the formulations of the invention are preferably made up into a sweet flavoured aqueous syrup formulation of generally conventional formulation (except for its novel amoxycillin : clavulanate ratio and intended use) containing a suitable weight of the amoxycillin and clavulanate in a unit dose volume, e.g. 5 ml or 2.5 ml of the syrup. Because of the water-sensitivity of clavulanate it is preferred to provide such a syrup formulation as dry powder or granules contained in an atmospheric moisture-proof container or sachet for make up with water or other suitable aqueous medium shortly prior to use.

The formulation of this invention will normally, in addition to its active materials amoxycillin trihydrate and potassium clavulanate, also include excipients which are standard in the field of formulations for oral dosing and used in generally standard proportions, and at generally standard particle sizes and grades etc.

In the case of paediatric oral suspensions, these excipients may comprise suspending aids, glidants (to aid filling), diluents, bulking agent, flavours, sweeteners,

stabilisers, and in the case of dry formulations for make up to an aqueous suspension, an edible desiccant to assist preservation of the potassium clavulanate against hydrolysis by atmospheric moisture on storage. Potassium clavulanate is normally supplied in admixture with silicon dioxide as diluent.

5 Suitable excipients for use include xantham gum (suspension aid), colloidal silica (glidant), succinic acid (stabiliser), aspartame (sweetener), hydroxypropyl-methylcellulose (suspension aid) and silicon dioxide (desiccant, diluent for potassium clavulanate and bulking agent). Flavours may comprise common flavours such as orange, banana, raspberry and golden syrup, or mixtures thereof, to suit local
10 requirements.

Generally the proportion of active materials amoxycillin trihydrate and potassium clavulanate in a dry formulation for make up with aqueous media into a solution, suspension or syrup formulation of the invention may be around 30-80 wt%.

15 The formulations of the invention may be adapted to paediatric dosing, i.e. to patients aged between 3 months to 12 years. Such formulations may be dosed in daily quantities up to the maximum normal permitted dose of amoxycillin and clavulanate.

A suitable dosage for paediatric patients is from 75 to 125mg/kg amoxycillin per day and from 12 to 18 mg/kg clavulanate per day. Preferably, the dosage is $35 \pm 10\%$, especially $\pm 5\%$, mg/kg amoxycillin and $5 \pm 10\%$, especially $\pm 5\%$, mg/kg
20 clavulanate (i.e. nominally a 7:1 ratio) administered tid.

A suitable dosage for older children and adult patients is from 2500 to 3250mg/kg amoxycillin per day and from 350 to 400 mg/kg clavulanate per day. Preferably, the dosage is $875 \pm 10\%$, especially $\pm 5\%$, mg amoxycillin and $125 \pm 10\%$, especially $\pm 5\%$, mg clavulanate (i.e. nominally a 7:1 ratio), or $1000 \pm 10\%$, especially
25 $\pm 5\%$, mg amoxycillin and $125 \pm 10\%$, especially $\pm 5\%$, mg clavulanate (i.e. nominally a 8:1 ratio), administered tid.

The formulation of the invention may for example be provided in solid unit dose forms embodying suitable quantities for the administration of such a daily dose. For example a unit dosage form may be tablets, or sachets containing granules or
30 powders for reconstitution, one or two of which are to be taken at each tid dosing interval. Alternatively a unit dose may be provided as a bulk of solid or solution or suspension, e.g. as a syrup for paediatric administration, together with a suitable measuring device of known type to facilitate administration of a suitable unit dose quantity of the formulation. A suitable unit dose quantity is one which enables the
35 administration of the above-mentioned daily dosage quantity divided between three tid doses.

For paediatric patients, a suitable unit dose quantity is preferably one which enables the administration of the above-mentioned daily dosage quantity in a volume

of a solution or suspension suitable for oral administration to a paediatric patient, preferably of between 2.5 to 10 ml, preferably as a syrup. A paediatric formulation may therefore comprise a bulk of a solution or suspension, e.g. a syrup, or granules or powder which can be made up into such a solution or suspension, at a concentration of
5 solution or suspension which contains such a dose in such a volume. Suitable such formulations are described in International application no PCT EP96/01881 (SmithKline Beecham).

For adults, a suitable unit dose may be provided in a tablet. A suitable tablet comprising 875mg amoxycillin and 125mg clavulanate is marketed by SmithKline
10 Beecham in several countries and is also described in WO 95/28927 (SmithKline Beecham).

Example 1 - Paediatric formulation

The formulations listed below were prepared as dry powder mixtures, using conventional techniques. The proportions of ingredients are expressed as mg/5ml dose of reconstituted aqueous suspension, the formulations nominally comprising either

5 200 or 400mg of amoxycillin per 5ml of dose:

Ingredient	mg/5ml	mg/5ml
amoxycillin trihydrate*	408.0	204.0
potassium clavulanate*	61.56	30.78
xanthan gum	12.5	12.5
colloidal silica	25.0	25.0
succinic acid	0.84	0.84
flavour	50.00	50.00
aspartame	12.50	12.50
hydroxypropylmethylcellulose	79.65	79.65
silicon dioxide	to 885.5	to 537.5

* expressed as free acid equivalent.

Example 2 - Tablet Formulation

10 A tablet formulation comprising 875mg amoxycillin and 125mg clavulanate was prepared having the following composition:

Ingredient	mg	wt. %
Active Constituents:		
Amoxycillin trihydrate	1017.4	70.2
(equivalent to amoxycillin)	875.00	
Potassium clavulanate	152.45	10.5
(equivalent to clavulanic acid)	125.0	
Other Constituents:		
Magnesium Stearate	14.50	1.00
Sodium Starch Glycollate	29.00	2.00
Colloidal Silicon Dioxide	10.0	0.70
Microcrystalline Cellulose	226.65	15.6
Core tablet weight	1450.00	100.00

15 The tablets are made by blending the amoxycillin, potassium clavulanate, and portions of microcrystalline cellulose and magnesium stearate, roller compacting this blend,

then blending with the other constituents, before tableting on a conventional tablet press and coating. The tablet core is coated with a film (Opadry White YS-1-7700/Opadry White OY-S-7300 ex Colorcon) from an aqueous solvent system, to give tablets with a nominal coated weight of 1482mg. Further details of how the tablets are manufactured are provided in WO 95/28927 (SmithKline Beecham).

Similar tablets can be made in which the roller compaction step is replaced by slugging and /or a final film coating is applied from an organic solvent system such as dichloromethane rather than an aqueous solvent system.

10

Claims

1. The use of amoxycillin and clavulanate in the manufacture of a medicament for the empiric treatment of infections potentially caused by DRSP which medicament comprises:
 - for an adult or older child patient, from 800 to 1100mg amoxycillin and from 100 to 150 mg clavulanate in a weight ratio between 6:1 and 10:1 inclusive; or
 - for a paediatric patient, from 30 to 40mg/kg body weight of amoxycillin and from 3 to 8 mg/kg body weight of clavulanate in a weight ratio between 6:1 and 10:1 inclusive;the medicament being taken three times a day (tid).
2. A use as claimed in claim 1 in which the ratio of amoxycillin to clavulanate is between 6.5 : 1 and 7.5 : 1 inclusive or 7.5:1 to 8.5:1.
3. A use as claimed in claim 1 in which the ratio of amoxycillin to clavulanate is about 7 : 1 or about 8:1.
4. A use as claimed in any one of claims 1 to 3 in which amoxycillin is in the form of amoxycillin trihydrate.
5. A use as claimed in any one of claims 1 to 4 in which clavulanate is in the form of potassium clavulanate.
6. A use as claimed in claim 1 in which the dosage quantity for paediatric patients is $35 \pm 10\%$ mg/kg amoxycillin and $5 \pm 10\%$ mg/kg clavulanate.
7. A use as claimed in claim 1 in which the dosage amount for an older child or an adult patient is $875 \pm 10\%$ mg amoxycillin and $125 \pm 10\%$ mg clavulanate or $1000 \pm 10\%$ mg amoxycillin and $125 \pm 10\%$ mg clavulanate.
8. A use as claimed in any one of claims 1 to 6 in which the formulation is adapted for administration to paediatric patients in the form of a powder or granular product for reconstitution into a suspension or solution and which comprises about 200mg/unit dose volume of amoxycillin and 28.6mg/unit dose volume of clavulanate or 400mg/unit dose volume of amoxycillin and 57.2mg/unit dose volume of clavulanate when reconstituted.

9. A use as claimed in any one of claims 1 to 5 or claim 7 in which the formulation is in the form of tablets and adapted to provide about 875mg amoxycillin and 125mg clavulanate per unit dose.
- 5 10. A method of treatment of infections potentially caused by DRSP which method comprises administering to a patient in need thereof a pharmaceutical formulation adapted for oral administration comprising either:
for an adult or older child patient from 800 to 1100mg amoxycillin and from 100 to 150 mg clavulanate in a weight ratio between 6:1 and 10:1 inclusive; or
- 10 for a paediatric patient from 30 to 40mg/kg body weight of amoxycillin and from 3 to 8 mg/kg body weight of clavulanate in a weight ratio between 6:1 and 10:1 inclusive; in combination with a pharmaceutically acceptable carrier or excipient, three times a day (tid).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02235

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/43 //(A61K31/43,31:42)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 28927 A (SMITHKLINE BEECHAM CORP ;SMITHKLINE BEECHAM PLC (GB); CONLEY CREIG) 2 November 1995 cited in the application * p.4, l.25-26; claims 1-17 *	1-10
X	JACOBSSON S ET AL: "EVALUATION OF AMOXICILLIN CLAVULANATE TWICE DAILY VERSUS THRICE DAILY IN THE TREATMENT OF OTITIS MEDIA IN CHILDREN" EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES, vol. 12, no. 5, 1 May 1993, pages 319-324, XP000576281 * par. bridging p.319-320; p.323, left hand col. the two last par. *	1-10
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

24 November 1997

Date of mailing of the international search report

16. 12. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Uiber, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02235

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	FELDMAN W ET AL: "TWICE-DAILY ANTIBIOTICS IN THE TREATMENT OF ACUTE OTITIS MEDIA: TRIMETHOPRIM- SULFANETHOXAZOLE VERSUS AMOXICILLIN-CLAVULANATE" CANADIAN MEDICAL ASSOCIATION JOURNAL, vol. 142, no. 2, 15 January 1990, pages 115-118, XP000576266 * p.118, left hand col., 1.5-10 *	1-10
P,Y	WO 96 34605 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US); BAX RICHARD) 7 November 1996 cited in the application * clinical trial- A and b; claims 1-31 *	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9528927 A	02-11-95	AP 564 A	21-11-96
		AU 2406895 A	16-11-95
		BG 100933 A	31-07-97
		CA 2188496 A	02-11-95
		CZ 9603090 A	16-04-97
		EP 0758235 A	19-02-97
		EP 0761218 A	12-03-97
		FI 964249 A	22-10-96
		HU 76335 A	28-08-97
		NO 964488 A	17-12-96
		PL 316966 A	03-03-97
		SK 135496 A	07-05-97
		ZA 9503236 A	27-12-95

WO 9634605 A	07-11-96	AU 5814096 A	21-11-96
